10:07:54 OCA PAD INITIATION - PROJECT HEADER INFORMATION 06/19/90

Active

Project #: E-25-M48 Cost share #: Rev #: 0
Center # : 10/24-6-Q5459-4A0 Center shr #: OCA file #:
Work type : RES
Contract#: 5 R29 HL39437-04 Mod #: Document : GRANT
Prime #: Contract entity: GIT

Subprojects ? : N
Main project #:

Project unit: ME Unit code: 02.010.126
Project director(s):
KU D N ME (404)894-6827

Sponsor/division names: DHHS/PHS/NIH / NATL INSTITUTES OF HEALTH
Sponsor/division codes: 108 / 001

Award period: 900801 to 910731 (performance) 911130 (reports)

Sponsor amount	New this change	Total to date
Contract value	103,327.00	103,327.00
Funded	103,327.00	103,327.00
Cost sharing amount		0.00

Does subcontracting plan apply ?: N

Title: HUMAN ATHEROSCLEROSIS: ROLE OF PULSATILE FLOW

PROJECT ADMINISTRATION DATA

OCA contact: Kathleen R. Ehlinger 894-4820

Sponsor technical contact

DR. EDWIN C. GANGLOFF
(301)496-1978

DIV OF HEART & VASCULAR DISEASES
NAT HEART,LUNG,& BLOOD INSTITUTE
BETHESDA, MD 20892

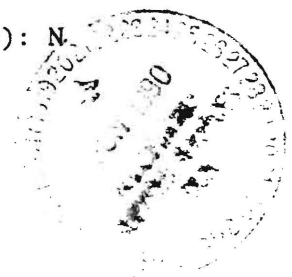
Sponsor issuing office

DORIS EAST
(301)496-7255

DIV OF EXTRAMURAL AFFAIRS
NATIONAL HEART, LUNG, & BLOOD INST.
BETHESDA, MD. 20892

Security class (U,C,S,TS) : U ONR resident rep. is ACO (Y/N): N
Defense priority rating : N/A NIH supplemental sheet
Equipment title vests with: Sponsor GIT X

Administrative comments -
INITIATION OF PROJECT. CONTINUATION OF E-25-M95.



GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 09/30/91

Project No. E-25-M48 Center No. 10/24-6-Q5459-4A0

Project Director KU D N School/Lab MECH ENGR

Sponsor DHHS/PHS/NIH/NATL INSTITUTES OF HEALTH

Contract/Grant No. 5 R29 HL39437-04 Contract Entity GIT

Prime Contract No.

Title HUMAN ATHEROSCLEROSIS: ROLE OF PULSATILE FLOW

Effective Completion Date 910731 (Performance) 911130 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	Y	
Final Report of Inventions and/or Subcontracts	N	
Government Property Inventory & Related Certificate	N	
Classified Material Certificate	N	
Release and Assignment	N	
Other	N	

CommentsON "FINAL" REPORTS REQUIRED; CONTINUED BY E-25-617.

Subproject Under Main Project No.

Continues Project No.

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	N
GTRC	Y
Project File	Y
Other	N
	N

SECTION 1 F-25-10148

Form approved through 3/31/91
OMB No. 0925-0001

472

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

APPLICATION FOR CONTINUATION GRANT

REVIEW GROUP	TYPE	ACTIVITY	GRANT NUMBER *(Insert on all pages)*
SB	5	R29	HL39437-05

TOTAL PROJECT PERIOD
From: 08/01/87 Through: 07/31/92

REQUESTED BUDGET PERIOD
From: 08/01/91 Through: 07/31/92

To be verified by applicant. Check information in items 1 through 6. If incorrect, furnish correct information in item 13.

1. TITLE OF PROJECT
HUMAN ATHEROSCLEROSIS: ROLE OF PULSATILE FLOW

2a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(name and address, street, city, state, zip code)*
KU, DAVID N
GEORGIA INSTITUTE OF TECHN
ATLANTA, GA 30332-0405

4. APPLICANT ORGANIZATION *(name and address, street, city, state, zip code)*
GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GA 30332-0420

5. ENTITY IDENTIFICATION NUMBER
158002023A1

2b. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
SCH OF MECHANICAL ENGINEERING

2c. MAJOR SUBDIVISION
COLLEGE OF ENGINEERING

3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR BIOMEDICAL RESEARCH SUPPORT GRANT *(see instructions)*
20 OTHER

6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION
CONTRACTING OFFICER
GEORGIA INSTIUTE OF TECHNOLOGY
ATLANTA, GA 30332-0420

Complete the following *(see instructions)*

7. HUMAN SUBJECTS
7a. ☒ NO ☐ YES { ☐ Exemption #_____ OR ☐ IRB Approval Date _____
7b. Assurance of Compliance #_____

8. VERTEBRATE ANIMALS
8a. ☒ NO ☐ YES ... IACUC Approval Date _____
8b. Animal Welfare Assurance # _____

9. PERFORMANCE SITE(S) *(organizations and addresses)*
School of Mechanical Engineering
Georgia Institute of Technology
Atlanta, Georgia 30332-0405

10. COSTS REQUESTED FOR BUDGET PERIOD
10a. DIRECT $ 66,688 | 10b. TOTAL $ 108,368

11. INVENTIONS *(see instructions)*
☒ NO ☐ YES { ☐ Previously reported OR ☐ Not previously reported

TELEPHONE INFORMATION

	AREA CODE	TELEPHONE NO. AND EXTENSION
12a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR *(Item 2a)* David N. Ku	404	894-6827
12b. NAME OF BUSINESS OFFICIAL *(Item 6)* Matt Gedney	404	894-4817
12c. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION *(Item 15)* Matt Gedney	404	894-4817

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWERS APPLY.

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense. *(U.S. Code, Title 18, Section 1001.)*	SIGNATURE OF PERSON NAMED IN 2a *(... acceptable)*	DATE 5/15/91
15. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense. *(U.S. Code, Title 18, Section 1001.)*	SIGNATURE OF PERSON NAMED IN 12c *(An ink "Per" signature not acceptable)*	DATE 5/15/91

RETURN COMPLETED APPLICATION TO PHS AS SOON AS POSSIBLE:
NO LATER THAN 1 JUN 1991

REQUESTED BUDGET FOR **NEXT BUDGET PERIOD** Follow instructions carefully	FROM 8/1/91	THROUGH 7/31/92	GRANT NUMBER R29H239437

A. ITEMIZE DIRECT COSTS REQUESTED FOR NEXT BUDGET PERIOD

PERSONNEL *(Applicant organization only)* NAME	ROLE IN PROJECT	1 TYPE APPT.	2 % OF APPT.	3 EFFORT ON PROJ.	DOLLAR AMOUNT REQUESTED *(Omit cents)* SALARY	FRINGE BENEFITS	TOTALS
David N. Ku	Principal Investigator	1.00	35	.35	30,635	8,057	38,692
Chris Markou	Postdoc Fellow	1.00	45	.45	12,393	3,259	15,652
Xiaoyi He	Grad Rsch Asst.	.33	100	.33	12,000		12,000
SUBTOTALS →					55,028	11,316	66,344

CONSULTANT COSTS *(See instructions)*

EQUIPMENT *(Itemize)*

SUPPLIES *(Itemize by category)*

Photo Supplies 344

344

TRAVEL	DOMESTIC	
	FOREIGN	
PATIENT CARE COSTS	INPATIENT	
	OUTPATIENT	

ALTERATIONS AND RENOVATIONS *(Itemize by category)*

CONSORTIUM/CONTRACTUAL COSTS *(See instructions)*

OTHER EXPENSES *(Itemize by category)*

TOTAL DIRECT COST *(Enter on Page 1, Item 10a)* → $ 66,688

B. SUPPLEMENTAL INFORMATION REGARDING *ITEMS* IN THE PROPOSED BUDGET FOR THE NEXT PERIOD WHICH REQUIRE EXPLANATION OR JUSTIFICATION.*(SEE INSTRUCTIONS)*

Due to unjustified budget cuts from N.I.H., the P. I. was reduced from 50% time to 35% time.

SECTION II **CURRENT BUDGET PERIOD AND KEY PERSONNEL**	FROM 8/1/91	THROUGH 7/31/92	GRANT NUMBER R29HL39437

The following pertains to your CURRENT PHS budget. This information will be used in determining the amount of support for the NEXT budget period.

A. CURRENT BUDGET	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (1)	ESTIMATED UNOBLIGATED BALANCE (2)	EXPLAIN ANY SIGNIFICANT ESTIMATED UNOBLIGATED BALANCE IN COLUMN 2 (3)
TOTAL DIRECT COSTS	63,579	0	N/A
INDIRECT COSTS *(As provided)*	39,748	0	N/A
TOTALS ——————————>	103,327	0	N/A

B. CURRENT BUDGET PERIOD KEY PERSONNEL ENGAGED ON PROJECT *(Only if different)*

NAME, DEGREE(S) SSN	POSITION TITLE AND ROLE IN PROJECT DEPARTMENT AND ORGANIZATION	CHANGE IN % OF EFFORT
N/A		

C. and D. *(Only if different)*
See instructions and provide the information required in Items C. and D. Use this page and continuation pages as necessary.

SECTION III. PROPOSED KEY PERSONNEL FOR THE **NEXT** BUDGET PERIOD *(Only if different)*

NAME, DEGREE(S), SSN	POSITION TITLE AND ROLE IN PROJECT	DEPARTMENT AND ORGANIZATION
N/A		

OTHER SUPPORT *(Use continuation pages if necessary)*	GRANT NUMBER R29HL39437

FOLLOW INSTRUCTIONS CAREFULLY. Incomplete, inaccurate, or ambiguous information about OTHER SUPPORT could lead to delays in the award.

For each of the key personnel, list in separate groups: (1) *all* currently active support; (2) *all* applications and proposals pending review or funding. Include *all* Federal, non-Federal, and institutional research, training, and other grant, contract, and fellowship support at the applicant organization and elsewhere. If none, state "none." If no changes from the application that was the basis for this submission, state "no change."

For each item give: (a) the source of support, identifying number and title; (b) percentage of appointment on the project; (c) dates of entire project period; (d) annual direct costs; and (e) a brief description of the project for non-PHS supported projects. If part of a larger project, identify the principal investigator/program director and provide (a) above for the parent project and (b) through (e) for the subproject.

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

(1) CURRENTLY ACTIVE SUPPORT: (a)

a. NSF "Presidential Young Investigator Award", EET 861657691
b. 0%
c. 9/1/87 - 8/30/92
d. $56,250
e. General Support of Laboratory

a. NIH "Human Atherosclerosis: Role of Pulsatile Flow", R29HL39437
b. 35%
c. 8/1/87 - 7/31/92
d. $63,596
e. This Grant

a. Whitaker Foundation "Magnetic Resonance Imaging of Blood Flow"
b. 20%
c. 5/1/89 - 4/30/92
d. $53,100
e. Develop MRI angiography

a. AHA "The Role of Shear Stress in the Development of Neointima and Pseudointima in Tapered PTFE Grafts"
b. 0%
c. 7/1/90 - 6/30/91
d. $30,000
e. Study Neointimal Hyperplasia

(2) Pending

a. NIH "Specialized Center of Research in Arteriosclerosis - Project 2"
b. 25%
c. 12/1/91 - 11/30/96
d. $71,340
e. Relate hemodynamics to lesion sites in a Pig model of atherosclerosis. There is no overlap with the current grant.

NOTE: NO PROGRAM INCOME IS ANTICIPATED FROM THIS PROJECT.

1. Summary of plans for next year of support

Specific Aims for next year:

1.Quantify the pulsatile flow field for post-prandial and exercise conditions in a model of the human abdominal aorta using magnetic resonance imaging,

2. Verify selected velocity measurements using MRI in a human aorta,

3. Correlate the hemodynamic parameters with raised plaque and intimal thickness obtained from pathology specimens.

Methods. In general, the methods for achieving the goals have been refined from the original grant proposal. Magnetic resonance velocimetry is now the preferred technique for measuring the complex three-dimensional velocities in the models. This technique can also be used to verify the hemodynamic assumptions through direct in vivo measurement. A new method has been developed to estimate the time varying wall shear stress in any artery. The time-varying wall shear stress can be approximated using an analytical solution for unsteady flow through straight tubes developed by Hale, McDonald and Wormersley. Through the use of recent mathematical software, this solution is easy to produce on a personal computer and a program has been developed to calculate the time-varying wall shear stress from the pulsatile flow rate in a vessel. Details of this computer solution are given in an attached manuscript. New computer graphics capabilities have been added to speed the analysis and correlation between the many hemodynamic and morphologic variables. Otherwise, the experimental design remains basically the same and the original objectives should be achieved.

2. RESULTS

The objective of this year's studies was to make quantitative measurements of velocity and wall shear stress for rest conditions in the model of the human abdominal aorta. Additionally, a new technique has been developed to calculate the unsteady shear stress at the wall from the centerline velocity or the total flow rate. Since the centerline velocity or flow waveform can be obtained by a number of non-invasive means (eg. ultrasound, plethysmography, MRI, a better estimate of oscillatory wall shear stress can now be made on an individual basis.

The Abdominal Aorta

As specified in the grant, the hemodynamic flow field in this complex part of the vasculature was quantified using a glass blown model of the aorta. To simulate exercise, the distal resistance to the legs was greatly reduced, and the cardiac output was doubled

of the sixteen time points throughout the cardiac cycle. Six shear stress measures were evaluated from the shear stress profiles. The mean shear stress was evaluated by taking the time average of the pulsatile shear stress values at each location around the circumference of the vessel. The maximum and minimum shear stress values were selected and subtracted to give the pulse shear stress. The percent of the cardiac cycle when the shear stress was negative (NEG) was evaluated, and an oscillatory shear index (OSI), which represents the amount of negative shear as a fraction of the total shear stress magnitude, was computed for the axially directed shear stress, with values ranging from 0 to 1.

Velocity profiles were taken at several locations along the aortic model. For the suprarenal aorta under normal resting conditions the shear stress changed during the cardiac cycle as shown in Figure 1a. The average mean shear stress values measured around the circumference was 1.3 dynes/cm^2, with a standard deviation of 0.6 dynes/cm^2. The spatial maximum, minimum and pulse shear stresses were 8.4, -4.1, and 12.5 dynes/cm^2 over the cardiac cycle.

In the infrarenal abdominal aorta, resting mean shear stress strongly oscillated along the posterior wall for much of the cycle shown in Figure 1b. At the posterior wall, the length of the reverse flow resulted in a time-averaged mean shear stress of -5.0 dynes/cm^2. The shear stress was negative for 75% of the cardiac cycle (NEG) and the OSI was 0.9. Elsewhere in the abdominal aorta, the mean shear stress was positive. The most negative shear stress value in the infrarenal aorta was -12.0 dynes/cm^2 at the posterior wall of the abdominal aorta and along the lateral posterior walls of the aortic bifurcation.

Shear stress measurements under simulated exercise conditions revealed that shear stress reversal was generally abolished throughout the abdominal aorta as depicted in Figure 2. The mean shear stresses were all positive at this location, ranging from 5.4 dynes/cm^2 at the posterior wall to 10.6 dynes/cm^2 at the left lateral wall. Only a very small area at the posterial experienced a short duration negative shear stress (-1.81 dynes/cm^2) at the posterior wall. The shear stress was negative for a maximum of 18% of the cardiac cycle in this region while OSI was 0.03 at the same location. Elsewhere in the aorta, NEG and OSI were zero.

Thus, the hemodynamic shear stress environment in the suprarenal aorta is fundamentally different from the infrarenal abdominal aorta and aortic bifurcation under resting conditions. For simulated exercise conditions, the overall mean shear stress becomes greater, and flow becomes much more linear with an elimination of most of the reversal of direction in wall shear stress.

The Superficial Femoral and Coronary Arteries

Atherosclerosis develops at two other important clinical sites: the superficial femoral artery (SFA) and the coronary arteries. Disease in the SFA is actually broad based and extends throughout this segment. Focal atherosclerosis in the coronary arteries represent the greatest cause of morbidity in the industrialized world.

The hemodynamics in the SFA is dominated by the pulsatile character of the flow waveform more than the simple geometry of this relatively straight vessel. The balance of the renal versus leg peripheral resistance creates a triphasic flow waveform pattern throughout the SFA by the same mechanism as in the abdominal aorta. For the superficial femoral artery, a pulsatile wall shear stress can be calculated from the flow waveform given in Figure 3. The mean shear stress through this artery was 5 dynes/cm^2 and the minimum shear stress was -20 dynes/cm^2. However, it is obvious that the shear stress oscillates around zero causing the shear forces to reverse direction through the cardiac cycle. The OSI for this arterial segment was 0.35 and NEG was 30%.

Hemodynamically, the coronary artery system is very difficult to simulate in vitro, being a branch flow on a moving surface. However, as a first approximation, one can use the calculated Wormersley solution to derive the unsteady wall shear stress for the coronary flow waveform. Flow through the left anterior descending (LAD) coronary artery is primarily diastolic. During systole, flow can actually reverse as blood is squeezed backwards from the myocardium. The coronary arteries can experience an oscillatory shear stress as illustrated in Figure 4. The mean shear stress was 10 dynes/cm^2, the minimum shear stress was -8 dynes/cm^2, the OSI was 0.06 and NEG was 7%. The hemodynamic wall shear stress in the LAD oscillates in direction and has a large negative shear stress at this site of important clinical disease.

Significance to atherogenesis. Locations of aortic atherosclerosis show a strong qualitative relation to the areas of oscillatory shear stress and low mean shear stress. Atherosclerosis in the abdominal aorta is generally confined to the infrarenal segment. The NHLBI sponsored Pathological Determinents of Atherosclerosis in Youth (PDAY) study of over 300 aortas has provided detailed probability of occurrence maps for raised plaque. The distribution of these plaques clearly indicates that the posterior section of the aorta and the lateral posterior portion of the aortic bifurcation are most diseased. Thus, in the abdominal aorta, locations of raised plaque appear to coincide well with the locations of low shear stress and areas of oscillating shear direction.

Other locations of atherosclerotic plaque such as the superficial femoral artery and the coronary arteries appear to be a specific site of significant oscillations in shear stress with transient negative shear stress less than -5 dynes/cm^2. Atherosclerotic plaque in the coronary generally consists of segmental disease which is more prevalent at the outer walls of the branch. In contrast, arteries typically free of disease are expected to experience biphasic flow with predominantly unidirectional shear stresses.

Hemodynamic forces likely play a critical role in the development of atherosclerosis. The detailed, physiologic, time-varying magnitudes and directions of these shear forces must be defined if we are to fully understand this complex disease. Future statistical correlations should help define the exact hemodynamic pattern responsible for atherognetic transformation.

These pulsatile shear conditions will have important ramifications on the evaluation of endothelial response to physiologic shear flows. Only through the quantification of

physiologic pulsatile arterial hemodynamics can one properly define the appropriate hemodynamic environment in which to study the biology of vascular cells. Without this information, irrelevant studies may be performed on the effects of non-physiologic mechanical stress on the vascular cells. The shear waveforms presented here will aid in the development of accurate hemodynamic environments for future cellular investigations.

3. The protocols for human subjects have not changed.

4. No vertebrate animal studies are involved.

5. Publications during the past year.

1. Ku, D.N., Zeigler, M., Stewart, M. "A study of predicted and experimental wall collapse in models of highly stenotic arteries." 2nd International Symposium on Biofluid Mechanics, (D. Liepsch, ed) Munich, Karger Scientific Publ., pp. 409-416, 1990.

2. Poiseau, E., Yoganathan, A., Ku, D.N., Dixon, T. "Magnetic resonance imaging of cardiac blood flow: An in vitro study." 2nd International Symposium on Biofluid Mechanics, (D. Liepsch, ed) Munich, Karger Scientific Pub., pp. 241-248, 1990.

3. Ku, D.N., Peifer, J., Biancheri, C., Pettigrew, R.I., Engles, H. "Potential Value of Magnetic Resonance Angiography in Patients with Vascular Disease", Current Critical Problems in Vascular Surgery (F.J. Veith, ed), Vol. II, pp. 36-41, 1990.

4. Ku, D.N., Zeigler, M.N., Downing, J.M., "One-dimensional steady inviscid flow through a stenotic collapsible tube," J. Biomechanical Engineering, Vol. 112, pp. 444-450, 1990.

5. Ku, D.N., Biancheri, C., Peifer, J., Markou, C., Engels, H., Pettigrew, R.I., "An evaluation of magnetic resonance velocimetry for steady flow", J. Biomechanical Engineering, Vol. 112, pp.464-472, 1990.

6. Oweida, S.W., Ku, D.N., Justicz, A.G., Burnson, G., Salam, A.A., "Hemodynamic consequences of carotid-carotid bypass for innominate artery stenosos." J. Vasc. Surgery, Vol. 13; pp. 416-422, 1991.

7. Oshinski, J., Biancheri, C., Ku, D.N., Markou, C., Pettigrew, R., Engles, H. "Phase velocity encoding of laminar and turbulent flow in a smooth stenosis and curved tube." Society for Magnetic Resonance Imaging, 8th Annual Meeting, Washington, D.C., 1990.

8. Peifer, J., Ku, D.N., Engels, H., Pettigrew, R., "Three-dimensional modeling of an abdominal aorta phantom from two MR images." Society for Magnetic Resonance Imaging, 8th Annual Meeting, Washington, D.C. 1990.

9. Ku, D.N., Pettigrew, R.I., Markou, C., Biancheri, C., "Fluid mechanical mechanisms of signal loss in MR images of flow through smooth and sharp stenoses," Society of Magnetic Resonance in Medicine, New York, 1990, Vol. 1, p. 226.

10. Ku, D.N., Markou, C., Oshinski, J., "Magnetic resonance imaging phase-velocity encoding measurements of secondary and separated flows." First World Congress of Biomechanics, San Diego, 1990, II-126.

11. Moore, J.E., Ku, D.N., "Initial flow velocimetry in a model of the human abdominal aorta." First World Congress of Biomechanics, San Diego, 1990, II-186.

12. Markou, C., Ku, D.N., "Accuracy of velocity measurements using Doppler ultrasound: A comparison between five signal analysis techniques." First World Congress of Biomechanics, San Diego, 1990, I-86.

13. Ku, D.N., "Hemodynamics and atherogenesis," Tutorial on Percutaneous Intra-Arterial Thrombolysis, Atlanta, 1990, 2-6.

14. Oshinski, J.N., Ku, D.N., Markou, C.P., Pettigrew, R.I., "Evaluation of the accuracy of MR phase-velocity imaging in straight tubes and stenosis," Journal of Magnetic Resonance Imaging, Vol. 1, p. 217, 1991.

15. McCord, B., Aoki, T., Ku,D.N., "Does cyclic stress cause fatigue of the atherosclerotic plaque?" World Congress on Medical Physics and Biomedical Engineering, Kyoto, Japan, 1991.

16. Downing, J.M., Ku, D.N., "The choking of viscous one-dimensional collapsible tube flow through a stenotic artery." World Congress on Medical Physics and Biomedical Engineering, Kyoto, Japan, 1991.

17. Moore, J.E., Jr., Ku, D.N., "Flow velocimetry in a model of the human abdominal aorta under simulated exercise condtions." World Congress on Medical Physics and Biomedical Engineering, Kyoto, Japan, 1991.

18. Aoki, T., Ku, D.N., "An analysis of the tube law for thick-walled eccentric arteries." ASME Winter Annual Meeting, 1991.

19. Powell, B., Ku, D.N., "The contribution of flow choking to dynamic stenosis resistance." ASME Winter Annual Meeting, 1991.

20. Oshinski, J.N., Ku, D.N., Pettigrew, R.I., Markou, C.P., "Effects of convective acceleration on the accuracy of fluid velocity measurements using phase velocity encoding." Society of Magnetic Resonance in Medicine, 1991.

21. McKinsey, J., McCord, B.N., Aoki, T., Ku, D.N., "Can mechanical stress cause fatigue of the atherosclerotic plaque?" Surgical Forum 1991.

In submission.

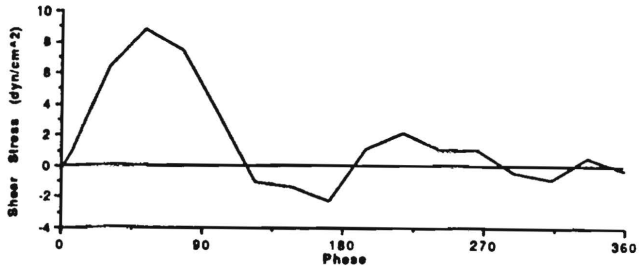
22. Moore, J.E., Jr., Ku, D.N., Zarins, C.K., Glagov, S. "Pulsatile flow visualization in the abdominal aorta under differing physiologic conditions: Implications for increased susceptibility to atherosclerosis."

23. Ku, D.N., Moore, J.E., Jr., He, Xiaoyi. "Oscillatory shear stress and atherosclerosis."

24. He, Xiaoyi, Ku, D. N., Moore, J. E., Jr. "Simple calculation of the velocity profiles for pulsatile flow in a blood vessel using Mathematica."

25. Aoki, T., Ku, D.N. "Collapse of diseased arteries with eccentric cross-section."

(a)



(b)

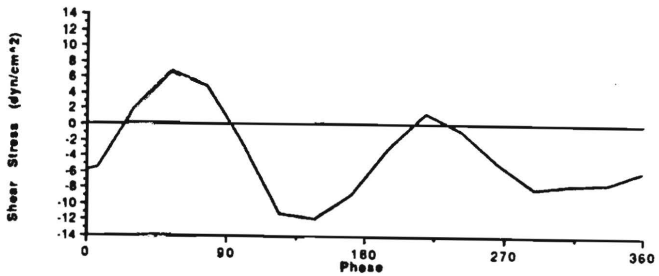
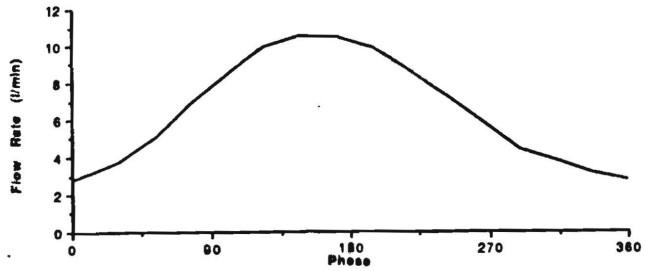


Figure 1

Shear stress waveforms for the suprarenal (a) and infrarenal (b) abdominal aorta. In the suprarenal aorta, the shear stress transiently reverses with a minimum value of only -2 dynes/cm^2. In contrast, the shear stress in the diseased infrarenal aorta, oscillates two times during the cycle with a minimum value of -12 dynes/cm^2.



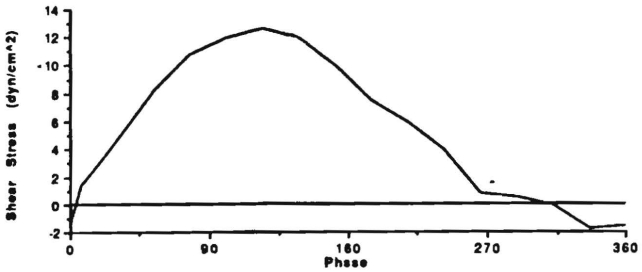
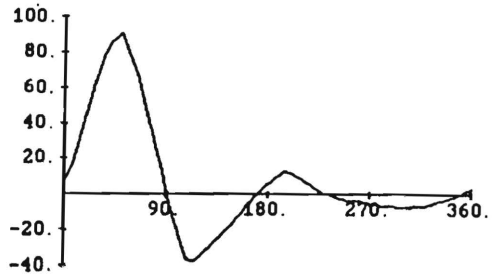
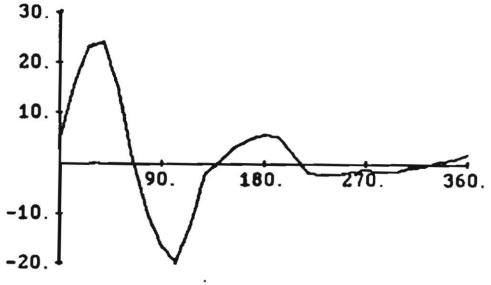


Figure 2

Shear stress versus time for exercise in the infrarenal abdominal aorta indicating the laminarization of flow and diminishing oscillatory nature of the waveform. The minimum value of shear under exercise conditions is only -2 dynes/cm^2.



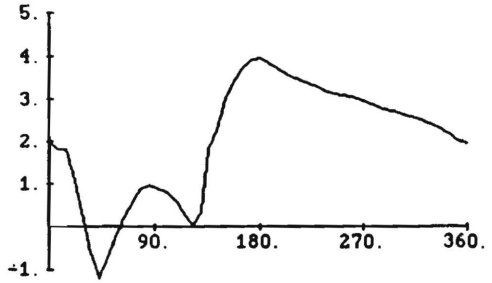
(a) centerline velocity (cm/s)



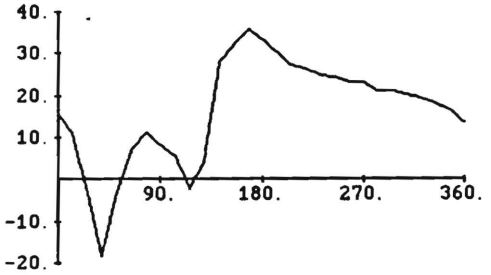
(b) Wall shear stress (dyn/cm^2)

Figure 3

Flow and shear stress waveforms for the superficial femoral artery estimated from the analytic solution of unsteady flow through a straight tube. The waveform oscillates around zero two times for the cardiac cycle with a minimum value of -20 dynes/cm^2 for the SFA.



(a) Flow rate (ml/s)



(b) Wall shear stress (dyn/cm^2)

Figure 4

Flow and shear stress waveforms for the left anterior descending coronary arteries. The LAD minimum value is -8 dynes/cm^2.

CHECKLIST	GRANT NUMBER HL39437-05

Check the appropriate boxes and provide the information requested. Make this page the last page of the signed original of the application. **Do not attach copies of this page to the duplicated copies of the application.**

ASSURANCES

The following certifications described below are made by checking the appropriate boxes and verified by the signature of the OFFICIAL SIGNING FOR APPLICANT ORGANIZATION on the FACE PAGE of the application.

a. **Delinquent Federal Debt.** ☒ No ☐ Yes (If "Yes," attach explanation.)

Before a grant award can be made, the applicant organization must certify that it is not delinquent on the repayment of any Federal debt. The certification applies to the applicant organization, not to the person signing the application as the authorized representative nor to the principal investigator/program director.

Examples of Federal debt include delinquent taxes, audit disallowances, guaranteed or direct student loans, FHA loans, business loans, and other miscellaneous administrative debts. For purposes of this certification, the following definitions of "delinquency" apply:

- For direct loans and fellowships (whether awarded directly to the applicant by the Federal Government or by an institution using Federal funds), a debt more than 31 days past due on a scheduled payment. (Definition excludes "service" payback under a National Research Service Award.)
- For guaranteed and insured loans, recipients of a loan guaranteed by the Federal Government that the Federal Government has repurchased from a lender because the borrower breached the loan agreement and is in default.
- For grants, organizations in receipt of a "Notice of Grants Cost Disallowance" which have not repaid the disallowed amount or which have not resolved the disallowance. (Definition excludes disallowances in an "appeal" status.)

Where the applicant discloses delinquency on debt to the Federal Government, the PHS shall (1) take such information into account when determining whether the prospective grantee organization is responsible with respect to that grant, and (2) consider not making the grant until payment is made or satisfactory arrangements are made with the agency to whom the debt is owed. Therefore, it may be necessary for the PHS to contact the applicant before a grant can be made to confirm the status of the debt and ascertain the payment arrangements for its liquidation. Applicants that fail to liquidate indebtedness to the Federal Government in a businesslike manner place themselves at risk of not receiving financial assistance from the PHS.

b. **Debarment and Suspension.** ☒ No ☐ Yes (If "Yes," attach explanation.)

Before a grant award can be made, the applicant organization must certify, among other things, that neither it nor its principals are presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from covered transactions by any Federal department or agency. Subawardees, that is, other corporations, partnerships, or other legal entities (called "lower tier" participants), must make the same certification to the applicant organization concerning their covered transactions. Please refer to the pertinent DHHS implementing regulations, Title 45 Code of Federal Regulations Part 76, for complete certification requirements.

c. **Drug-Free Workplace.** ☒ Yes ☐ No (If "No," attach explanation.)

Before a grant award can be made, the applicant organization must certify that it will provide a drug-free workplace. The main points of the certification require the applicant organization to:

- Publish a statement notifying employees that the unlawful manufacture, distribution, dispensation, possession, or use of a controlled substance is prohibited in the workplace and specifying the actions that will be taken against employees for violation of such prohibition;
- Establish a drug-free awareness program;
- Require that each employee engaged in the performance of a grant or contract be provided a copy of the published statement;
- Notify the employee that as a condition of employment, the employee will abide by the terms of the statement;
- Notify the PHS awarding component of any employee convicted of a drug violation occurring in the workplace; and
- Require any employee who is convicted of a drug offense occurring in the workplace to participate in a rehabilitation program.

Please refer to the pertinent DHHS implementing regulations, Title 45 Code of Federal Regulations Part 76, for complete certification requirements.

INDIRECT COST CALCULATION

Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHHS Regional Office, or, in the case of for-profit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. Indirect costs will not be paid on foreign grants, construction grants, grants to Federal organizations and grants to individuals, and usually not on conference grants. Follow any additional instructions provided for Research Career Development Awards, Institutional National Research Service Awards, and specialized grant applications.

☐ DHHS Agreement Dated: _____ ☐ No Indirect Costs Requested

☐ No DHHS Agreement, but rates established with ONR DATE 6/1/90

***CALCULATION**

Enter proposed budget period:

Amount of Base $ 66,688 x Rate Applied 62.5% % = Indirect Costs $ 41,680

Add to total direct costs from page 2 and enter new total on FACE PAGE, Item 10b

*Check appropriate box(es)

☐ Salary and wage base ☐ Modified total direct costs base ☐ Other base (Attach explanation)

☐ Off-site, other special rate, or more than one rate involved (Attach explanation)

*This is the required last page of the application.